REMARKS

Claims 5-12 and 14-61 are currently pending in this application. Claims 1-4 and 13 were previously canceled. Claims 39-43 and 47-60 are withdrawn from consideration. Claims 5-12, 14-38, 44-46, and 61 are under consideration. Claims 5-12, 14-27, 32-39, 44-46, and 61 have been rejected. Applicants acknowledge that the Examiner has allowed claims 37 and 38. The Examiner provided no grounds for rejection of claims 28-31 and 36; Applicants therefore respectfully request confirmation thereof.

Claims 5-10, 12, 16, 22-25, 27, 32, 34, and 61 are hereby canceled. Claims 11, 17-21, 26, 28-29, 33, 35, 36, and 44 have been amended. Reconsideration and allowance of the application in light of the foregoing amendments and the following remarks are respectfully requested.

Withdrawn Claim Rejections Under 35 USC §112, Second Paragraph

A) The Examiner stated on page 2 of the Office Action that the rejection of claims 6-10, 12, 16-21, and 24 under 35 USC §112, second paragraph for the recitation of "IL-18 activity" and "neutralizing antibody" has been withdrawn.

B) The Examiner stated on page 2 of the Office Action that claims 5-12, 14-21, and 24 are indefinite in the recitation of "KG1" and stated that amendment of the claims to recite "KG-1" and to include the appropriate ATCC Accession Number would obviate this rejection.

Not in acquiescence of the rejection but in order to expedite allowance of the claims, claims 5-10, 12, 16, and 24 have been canceled and claims 11, and 17-21 have been amended to recite "KG-1" and to include the ATCC Accession Number "ATCC-CCL-246". In view of the foregoing amendments and remarks, Applicants respectfully request removal of the rejection of claims 5-12, 14-21, and 24 under 35 USC §112, second paragraph.

Claim Rejections Under 35 USC §112, First Paragraph

The Examiner rejected claims 5-12, 14-21, and 24 under 35 USC §112, first paragraph, as containing subject matter that is not enabled. The Examiner requested that Applicants provide evidence that the KG-1 cell line (ATCC Accession Number ATCC-CCL-246) is publicly available. Applicants

attached herewith tat Appendix A a printout from the ATCC website containing the public ordering information for the KG-1 cell line.

In view of the foregoing remarks, Applicants respectfully request the removal of the rejection of claims 5-12, 14-21, and 24 under 35 under 35 USC §112, first paragraph.

The Examiner rejected claims 23-27 and 32-35 under 35 USC §112, first paragraph, contending that the claims are not enabled because changes in the amino acid composition of the antibodies of the invention would require undue experimentation to test. Applicants traverse the rejections to the extent it is maintained over the claims as amended.

Not in acquiescence of the rejection but in order to expedite allowance of the claims, Applicants have canceled claims 23-25, 27, 32, and 34 and have amended claims 26, 33, and 35 to require all three CDRs for either the heavy or light chain variable region and that any amino acid modifications take place at specific amino acid positions within each CDR. Therefore, for antibody 2E1, at most there can be 5 amino acid modifications in HCDR1, 6 amino acid modifications in HCDR2, 4 amino acid modification in HCDR3, 4 amino acid modifications in LCDR1, 4 amino acid modifications in LCDR2, and 11 amino acid modification in HCDR3, providing that the modification(s) does not inhibit IL-18 binding to the epitope comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 33. For antibody LT28, at most there can be 4 amino acid modifications in HCDR1, 8 amino acid modifications in HCDR2, 9 amino acid modification in HCDR3, 4 amino acid modifications in LCDR1, 4 amino acid modifications in LCDR2, and 11 amino acid modification in HCDR3, providing that the modification(s) does not inhibit IL-18 binding. Contrary to the Examiner's contention that the changes in amino acid composition would require undue experimentation to test, Applicants respectfully submit that such experimentation is routine and that Applicants seek appropriate breadth in the claims, for example, so that competitors cannot simply alter one or more amino acids in order to design around a claim requiring a specific amino acid sequence. In particular, Applicants submit that they have identified the epitopes comprising an amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 33 and believe they have enabled antibodies that bind to those epitopes and that contain the 3 CDRs sequences as defined by the claims, whether or not they are slightly altered, wherein such alterations are limited to those that would allow the antibody or binding portion thereof to still bind to the epitope comprising an amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 33.

In view of the foregoing amendments and remarks, Applicants respectfully request the removal of the rejection of claims 23-27 and 32-35 under 35 USC §112, first paragraph.

Claim Rejections Under 35 USC §103(a)

The Examiner rejected claims 4-12, 14-24, 44-46 and 61 under 35 USC §103(a) as being unpatentable over Kucherlapati et al. (US Patent No. 6,075,181) and Dinarello et al. (J. Leukoc. Biol. 1998; 63:658-664). Applicants respectfully submit that claim 4 was canceled in the amendment filed on August 11, 2005 and therefore no longer under consideration. Applicants respectfully submit that claims 5-10, 12, 16, 22-24, and 61 have been canceled. Applicants therefore traverse the rejection as it relates to pending independent claim 11 and claims that depend therefrom, namely, claims 14, 15, 17-21, and 44-46, to the extent the rejections are maintained over the claims as amended.

Applicants submit that the above-cited references, either singularly or in combination, do not teach, suggest, or motivate one skilled in the art, to make Applicants' human anti-IL-18 antibodies or methods of making the same as recited by the claims as amended.

Dinarello et al. and Kucherlapati et al., either alone or in combination, do not teach or suggest fully human antibodies to human IL-18, nor do Dinarello et al. and Kucherlapati et al. set forth which epitopes such antibodies might be bound to or the dissociation constants and activity of the antibodies generated. In particular, as required by claim 11 and claims dependent therefrom, Dinarello et al. and Kucherlapati et al. do not teach or suggest an isolated human antibody, or an antigen-binding portion thereof, that binds an epitope of human IL-18, or portion thereof, the epitope comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 33, wherein the antibody, or antigen-binding portion thereof, dissociates from the epitope of human IL-18 with a k_{off} rate constant of $0.1s^{-1}$ or less, as determined by surface plasmon resonance, or inhibits human IL-18 activity of IFN-γ induction in KG-1 cells (ATCC Accession No. ATCC-CCL-246) with an IC_{50} of 1×10^{-6}M or less.

In addition, Dinarello et al. and Kucherlapati et al., either alone or in combination, do not teach a human anti-IL-18 antibody that dissociates from human IL-18 with a k_{off} rate constant of $0.1s^{-1}$or less, $1 \times 10^{-2}s^{-1}$or less, $1 \times 10^{-3}s^{-1}$or less, $1 \times 10^{-4}s^{-1}$or less, $1 \times 10^{-5}s^{-1}$or less, or $1 \times 10^{-6}s^{-1}$or less as determined by surface plasmon resonance, as required by pending claims 17-21 and 44-46. Further, Dinarello et al. and Kucherlapati et al., either alone or in combination, do not teach an anti-IL-18 antibody that inhibits human IL-18 activity of IFN-γ induction in KG-1 cells with an IC_{50} of 1×10^{-6}M or less, 1×10^{-7}M or

less, 1 x 10^{-8}M or less, 1 x 10^{-9}M or less, 1 x 10^{-10}M or less, or 1 x 10^{-11}M or less, as required by claims 17-21 and 44-46. Still further, Dinarello et al and Kucherlapati et al., either alone or in combination, do not teach a human IL-18 antibody that binds an epitope of human IL-18 comprising an amino acid sequence of either SEQ ID NO: 3 or 33 as required by claims 11, 14, 15, 17-21, and 44-46.

In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejection of claims 11, 14, 15, 17-21, and 44-46 under 35 USC §103(a).

Conclusion

In view of the foregoing amendments and remarks, Applicants believe that the rejections set forth in the Office Action dated 12 August 2008 have been overcome and consequently that all claims are in condition for allowance. Applicants, therefore, respectfully request reconsideration and removal of the rejections, and allowance of the claims as amended.

Respectfully submitted,

Date: Dec. 11, 2008

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Cell Biology

ATCC® Number:	**CCL-246™** Order this Item	**Price:**	**$244.00**
Designations:	KG-1	**Depositors:**	DW Golc
Biosafety Level:	1	**Shipped:**	frozen
Medium & Serum:	See Propagation	**Growth Properties:**	suspensi
Organism:	*Homo sapiens* (human)	**Morphology:**	myelobla
Source:	**Organ:** bone marrow **Disease:** acute myelogenous leukemia		
Cellular Products:	HLA DR		
Permits/Forms:	In addition to the MTA mentioned above, other ATCC and/or regulatory permits may be rec of this ATCC material. Anyone purchasing ATCC material is ultimately responsible for o Please click here for information regarding the specific requirements for shipment to your l		
			Related Ce
Applications:	transfection host(technology from amaxa)		
Reverse Transcript:	negative		
Antigen Expression:	HLA A30, A31, B35, Cw4		
DNA Profile (STR):	Amelogenin: X,Y CSF1PO: 7 D13S317: 11,12 D16S539: 10,11 D5S818: 13 D7S820: 8,10 THO1: 7,8 TPOX: 7,9 vWA: 14,19		
Cytogenetic Analysis:	The stemline chromosome number is near-diploid, with the 2S component occurring at (constitutive markers) were common to most, if not all, metaphases analyzed. Modal chror (or 46 plus a small metacentric chromosome which is smaller than the G1 group cl chromosomes 5, 7, 8, 12 and 17 were monosomic, and others were disomic. The Y chron the Q-banded preparations.		
Isoenzymes:	AK-1, 0		

	ES-D, 1 G6PD, B GLO-I, 2 Me-2, 1 PGM1, 1-2 PGM3, 0
Age:	59 years
Gender:	male
Ethnicity:	Caucasian
Comments:	The KG-1 cell line was derived by H.P. Koeffler and D.W. Golde. A bone marrow aspirate 59-year-old Caucasian male with erythroleukemia that evolved into acute myelogenous leu KG-1 cells spontaneously differentiate to granulocyte and macrophage like cells. They show a good response to colony stimulating factor (CSF). [1056] The line is EBNA negative (EBNA-).
Propagation:	**ATCC complete growth medium:** The base medium for this cell line is ATCC-formul Dulbecco's Medium, Catalog No. 30-2005. To make the complete growth medium, add the to the base medium: fetal bovine serum to a final concentration of 20%. **Temperature:** 37.0°C
Subculturing:	**Protocol:** Cultures can be maintained by the addition of fresh medium or replacement of cultures can be established by centrifugation with subsequent resuspension at 2 X 1 Maintain cell density between 2 X 10(5) and 1 X 10(6) viable cells/ml. Do not allow cells/ml. **Medium Renewal:** Twice per week
Preservation:	**Freeze medium:** Complete growth medium supplemented with 5% (v/v) DMSO **Storage temperature:** liquid nitrogen vapor phase
Related Products:	Recommended medium (without the additional supplements or serum described under AT 2005 recommended serum:ATCC 30-2020
References:	867: Koeffler HP, Golde DW. Human myeloid leukemia cell lines: a review. Blood 56: 34 6996765 1056: Koeffler HP, Golde DW. Acute myelogenous leukemia: a human cell line responsive activity. Science 200: 1153-1154, 1978. PubMed: 306682 26069: . . Blood 54: 174a, 1979. 33055: Penrose JF, et al. Molecular cloning of the gene for human leukotriene C4 synthas 11356-11361, 1996. PubMed: 8626689

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